REMARKS

I. Introduction

Applicants acknowledge their receipt of the Office Action mailed on January 12, 2007. Applicants now respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

II. Status of the Claims and Summary of Amendments Thereto

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claims 1-135 and 137-139 have been cancelled without prejudice or disclaimer thereof.

Claims 136, 164, 179, 180-182 and 192 are currently being amended.

Claims 194-248 and 249-303 are being added.

After amending the claims as set forth above, claims 136 and 140-303 are now pending in this application.

Claims 136 and 179 have been amended to recite a "D50" particle size for the fenofibrate composition of less than about 500 nm. *See* page 30, line 18, through page 31, line 5. Claim 164 has been amended to similarly recite a "D50" particle size, to delete the recitation of particle sizes greater than about 500 nm, and to add a particles size of "about 150 nm or less." *See* page 30, lines 25-26. Claims 180-182 have also been amended to recite a D50 particle size, and claim 192 has been amended to omit reference to a trademark/trade name.

New claims 194-248 correlate to claims 136 and 140-193 except that independent claim 194 recites "a mean particle size of less than about 500 nm" (instead of a D50 particle size). Similarly, new claims 249-303 correlate to claims 136 and 140-193 except that

independent claim 249 recites "a D90 particle size of less than about 700 nm" (instead of a D50 particle size). Support for the new claims can be found in the application, for example at page 30, line 18, through page 31, line 18; Table 1, page 40; Table 4, page 42.

For the Examiner's convenience, the table below summarizes the relationship between the pending and new claims.

Claim Set	Broadest Particle Size Definition in the Independent Claim
Claim Set #1 includes claims 136 and 140-193	D50 particle size of less than about 500 nm
Claim Set #2 includes claims 194-248	Mean particle size of less than about 500 nm
Claim Set #3 includes claims 249-303	D90 particle size of less than about 700 nm

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

III. Claim Objections

The Office Action objected to claim 192 for reciting the "trademark/trade name POLYQUAT™, MIRAPOL™ and ALKAQUAT™." These terms have been deleted, thereby obviating the objection.

IV. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 136 and 140-193 have been rejected as allegedly containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the Art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Office Action at page 3.) Applicants respectfully traverse this ground for rejection.

A. In contrast to the Examiner's Assertion, Applicants Teach More than One Composition Encompassed by the Claimed Invention

In support of this ground for rejection, the Examiner alleged that "[t]he specification provides a written description of only a single stable fenofibrate composition which meets the functional limitations and is termed 'TRICOR®.'" (Office Action at page 4.)

Applicants first note that as used in the application, the term "TRICOR®" refers to the prior art microcrystalline fenofibrate composition, and not to the compositions encompassed by the claimed invention. *See e.g.*, page 7, lines 21-23, of the application. In the Office Action, the Examiner incorrectly identified the compositions of the invention as "TRICOR®" formulations.

Second, the Examiner's allegation that the application teaches "only one species" encompassed by the claimed invention is false. Specifically, as described in more detail below, Applicants give several examples of compositions that fall within the scope of the claims. For instance, at least Formulation 1 of Example 1, Formulation 4 of Example 2, the two compositions of Example 3, the composition of Example 4, the composition of Examples 5 and 6, and the composition of Examples 7 and 8 meet the limitations of the claims.

B. Testing in Simulated Biological Fluids is Predictive of In Vivo Success, Which Means That Testing in Simulated Biological Fluids can be Predictive of Compositions That Meet the Claim Limitations

Applicants teach multiple exemplary compositions that meet the C_{max} and AUC parameters of the claims as determined by: (1) *in vitro* testing in simulated biological fluids, such as simulated intestinal fluid, and (2) *in vivo* testing. As taught in the application, "[t]esting in fluids representing electrolyte fluids is useful as such fluids are representative of physiological conditions found in the human body." *See* page 40, lines 16-17; and page 41, lines 3-5, of the application.

Testing in simulated biological fluids as a predictor of *in vivo* performance is also described in co-owned U.S. Patent Publication No. US-2004-0029099-A1, for *In vitro* Methods for Evaluating the *In vivo* Effectiveness of Dosage Forms of Microparticulate or Nanoparticulate Active Agent Compositions." *See e.g.*, paragraph 15 of US-2004-0029099-

A1 which states that "the *in vivo* effectiveness of dosage forms of nanoparticulate and microparticulate poorly water soluble active agents can be reliably predicted by utilizing an *in vitro* redispersibility test. The redispersibility test employs biorelevant aqueous media that mimic human physiological conditions . . ."

The redispersibility test is a quantitative measure of the ability of a formulation to regenerate particle sizes that are optimum *in vivo*. Such regenerated particle sizes are generally similar to the primary active agent particle size present prior to formulating the active agent into a dosage form. For example, if a nanoparticulate active agent dispersion is used to make the dosage form, then the primary active agent particle size is that present in the dispersion. The test employs biorelevant aqueous media which mimic *in vivo* human physiological conditions, such as the ionic strength and pH found *in vivo*. Such biorelevant aqueous media can be electrolyte solutions, such as HCl or NaCl solutions, or solutions of other salts and acids, or combinations thereof, which have the desired biorelevant characteristics. *See* paragraph 15 of US-2004-0029099-A1.

This is the same test utilized in the present application to predict the *in vivo* properties of fenofibrate compositions. US-2004-0029099-A1 is relied upon not to enable the claimed invention, but to provide additional validation of the techniques disclosed in the application regarding identifying fenofibrate compositions that meet the claim limitations using *in vitro* redispersibility testing in simulated biological fluids.

Redispersibility properties of a nanoparticulate based dosage form are especially important, because when the dosage form of a nanoparticulate active agent does not suitably redisperse following administration, the benefits of formulating the active agent into nanoparticles, such as the C_{max} and AUC profiles recited in Applicants' claims, may be compromised or altogether lost. This is because in the absence of redispersibility the dosage form produces clumps or large aggregates of particles, and not discrete nanoparticles of active agent.

C. Exemplary Compositions Disclosed in the Application That Meet Applicants' Claim Limitations

Attached is a chart of compositions disclosed in the application that meet Applicants' claim limitations. *See* Section A of the attached table (EXHIBIT 1). Also taught are compositions which *do not* meet the claim limitations, thereby providing guidance to the practitioner as to identifying additional compositions that fall within the scope of the claims. *See* Section B of the attached table (EXHIBIT 1).

The compositions which meet Applicants' claim limitations, described in detail below, differ in one or more of the following parameters: (1) the amount of fenofibrate; (2) the identify of one or more surface stabilizers; and/or (3) the quantity of one or more surface stabilizers. All of the compositions are also described in Section A of the attached table (EXHIBIT 1).

1. First Exemplary Composition That Meets Applicants' Claim Limitations

The first described fenofibrate composition which meets the limitations of Applicants' claims is disclosed in Example 1. Example 1, Formulation 1, describes a composition comprising 5% fenofibrate, 1% hypromellose, and 0.05% dioctyl sodium sulfosuccinate (all amounts w/w). Application at page 40, Table 1. The mean particle size of the formulation was 139 nm, with 90% of the particles having a size of less than 266 nm (*i.e.*, a "D90"). Application at page 40, Table 1. Redispersion testing showed that in three different simulated biological fluids (electrolyte test media #1, #2, #3), two showed no agglomeration and one showed slight particle agglomeration. Application at page 40, Table 2. After 2 weeks storage in water, the composition had a mean particle size of 295 nm, and a D90 of less than 386 nm, demonstrating a stable composition. Application at page 41, Table 3. These successful redispersion testing results, showing minimal or no particle agglomeration in simulated biological fluids, are predictive of the *in vivo* success of this composition in meeting Applicants' claim limitations regarding C_{max} and AUC.

2. Second Exemplary Composition That Meets Applicants' Claim Limitations

The second described fenofibrate composition which meets the limitations of Applicants' claims is disclosed in Example 2. Specifically, Example 2, Formulation 4,

describes a composition comprising 5% fenofibrate, 1% hypromellose, and 0.01% dioctyl sodium sulfosuccinate (all amounts w/w). Application at page 41, lines 15-16. The mean particle size of the formulation was 412 nm, with 90% of the particles having a size less of than 502 nm. Application at page 42, Table 4. Redispersion testing showed that in three different simulated biological fluids (electrolyte test media #1, #2, #3), no agglomeration was observed. Application at page 42, Table 5. These successful redispersion testing results, showing no particle agglomeration in simulated biological fluids, are predictive of the *in vivo* success of this composition in meeting Applicants' claim limitations regarding C_{max} and AUC.

3. Third Exemplary Composition That Meets Applicants' Claim Limitations

The third described fenofibrate composition which meets the limitations of Applicants' claims is disclosed in Example 3. Example 3 describes two compositions comprising fenofibrate. The first composition comprises fenofibrate and sucrose in a ratio of 1:0.6, and hypromellose and dioctyl sodium sulfosuccinate in a ratio of 1:0.2. Application at page 43, Table 6. Redispersibility was tested in water and two different electrolyte solutions. Application at page 43, Table 6. In water, the redispersed mean particle size was 390 nm, with 90% of the fenofibrate particles having a size of less than 374 nm, and 99.7% of the fenofibrate particles having a size of less than 1 micron. Application at page 43, Table 6. In Electrolyte media #2 and #3, the mean size of the redispersed fenofibrate particles was 258 and 287 nm, the D90 was 374 and 430 nm, and 99.7 and 99.6% of the fenofibrate particles were less than 1 micron, respectively. Application at page 43, Table 6. These successful redispersion testing results, showing minimal or no particle agglomeration in simulated biological fluids, are predictive of the *in vivo* success of this composition in meeting Applicants' claim limitations regarding C_{max} and AUC.

4. Fourth Exemplary Composition That Meets Applicants' Claim Limitations

The fourth described fenofibrate composition which meets the limitations of Applicants' claims is disclosed in Example 3. Example 3 describes two compositions comprising fenofibrate. The first composition was described above. The second composition comprises fenofibrate and sucrose in a ratio of 1:1, and hypromellose to dioctyl sodium

sulfosuccinate and sodium lauryl sulfate in a ratio of 1:0.3. Application at page 43, Table 6. Redispersibility was tested in water and two different electrolyte solutions. Application at page 43, Table 6. In water, the redispersed mean particle size was 182 nm, with 90% of the fenofibrate particles having a size of less than 260 nm, and 100% of the fenofibrate particles having a size of less than 1 micron. Application at page 43, Table 6. In Electrolyte media #2 and #3, the mean size of the redispersed fenofibrate particles was 193 and 258 nm, the D90 was 276 and 315 nm, and 100% of the fenofibrate particles of both compositions were less than 1 micron. Application at page 43, Table 6. These successful redispersion testing results, showing minimal or no particle agglomeration in simulated biological fluids, are predictive of the *in vivo* success of this composition in meeting Applicants' claim limitations regarding C_{max} and AUC.

5. Fifth Exemplary Composition That Meets Applicants' Claim Limitations

The fifth described fenofibrate composition which meets the limitations of Applicants' claims is disclosed in Example 4. Example 4 describes a composition comprising fenofibrate and sucrose in a ratio of 1:1 and hypromellose to dioctyl sodium sulfosuccinate and sodium lauryl sulfate in a ratio of 1:0.45. Application at page 44, Table 7. Redispersibility was tested in water and two different electrolyte solutions. In water, the redispersed mean particle size was 196 nm, with 90% of the fenofibrate particles having a size of less than 280 nm, and 100% of the particles less than 1 micron. Application at page 44, Table 7. In Electrolyte media #2 and #3, the mean size of the redispersed fenofibrate particles was 222, the D90 was 306, and 100% of the fenofibrate particles were less than 1 micron. Application at page 44, Table 7. These successful redispersion testing results, showing minimal or no particle agglomeration in simulated biological fluids, are predictive of the *in vivo* success of this composition in meeting Applicants' claim limitations regarding C_{max} and AUC.

6. Sixth Exemplary Composition That Meets Applicants' Claim Limitations

The sixth described fenofibrate composition which meets the limitations of Applicants' claims is disclosed in Examples 5 and 6. Example 5 describes a composition comprising 160 mg of fenofibrate in combination with hypromellose, dioctyl sodium

sulfosuccinate, and sodium lauryl sulfate. *See* page 44, line 12, through page 46, line 8, of the application (describing preparation of the fenofibrate composition). The mean fenofibrate particle size of the composition was 169 nm. Application at page 44, line 17, through page 45, line 2. Example 6 describes *in vivo* human testing demonstrating that the fenofibrate composition meets the C_{max} and AUC limitations of Applicants' claims.

7. Seventh Exemplary Composition That Meets Applicants' Claim Limitations

The seventh described fenofibrate composition which meets the limitations of Applicants' claims is disclosed in Examples 7 and 8. Example 7 describes preparation of a 145 mg fenofibrate tablet according to the invention, comprising hypromellose, dioctyl sodium sulfosuccinate, and sodium lauryl sulfate. The composition of the 145 mg tablet is shown in Table 18, page 52 of the application. Example 8 describes comparison of the dissolution of the prior art microparticulate TRICOR® fenofibrate tablet with the 145 mg fenofibrate tablet prepared in Example 7. Dissolution was conducted in media representative of *in vivo* conditions; *i.e.*, "the dissolution medium is predictive of *in vivo* dissolution of a composition." Application at page 53, lines 3-6 and 10-11. In twelve test samples, the mean dissolution for the 145 mg fenofibrate tablet at 5, 10, 20, and 30 minutes was 41.7%, 82.6%, 100.5%, and 102.0%, respectively. In contrast, the conventional, microcrystalline TRICOR® tablet showed a mean dissolution at 5, 10, 20 and 30 minutes of 10, 20, 50, and 75%, respectively. These successful redispersion testing results for the 145 mg fenofibrate tablet, showing complete dissolution in simulated biological fluids (which is equivalent to no particle agglomeration), are predictive of the *in vivo* success of this composition in meeting Applicants' claim limitations regarding C_{max} and AUC.

D. Applicants' Have Met Their Burden Under 35 U.S.C. § 112, First Paragraph, for Providing a Written Description of the Claimed Invention

The first paragraph of 35 U.S.C. § 112 requires that the "specification shall contain a written description of the invention...." To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See e.g., Moba, B.V. v. Diamond Automation, Inc.*, 66 USPQ2d 1429, 1438 (Fed.

Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). In addition, to satisfy the first paragraph requirement of 35 U.S.C. § 112, the original application must provide "adequate support" for the claims at issue. Applicants' have satisfied both requirements, as discussed below.

1. Applicants' Specification Demonstrates Possession of the Claimed Invention

The "possession" element of the written description requirement of 35 U.S.C. § 112, first paragraph, may be shown in a variety of ways, including description of an actual reduction to practice. *See e.g., Pfaff v. Wells Elecs., Inc.*, 48 USPQ2d 1641, 1647 (1998); *Amgen, Inc. v. Chugai Pharmaceutical*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). Thus, "possession" of a composition claim may be satisfied via description of a representative number of compositions that fall within the scope of the claim. *See* M.P.E.P. 2163, Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, Section II.A.3.(a) "For each claim drawn to a genus."

The compositions detailed above are representative of Applicants' claimed composition, as they differ in at least one of: (1) the quantity of fenofibrate present; (2) the identify of one or more surface stabilizers present; and (3) the quantity of one or more surface stabilizers present. Thus, Applicants have satisfied their burden of establishing that they had possession of the claimed invention as of the earliest claimed priority date.

2. Applicants' Specification Provides Written Support for the Claimed Invention

A description satisfying the first paragraph, 35 U.S.C. 112 requirement may be in the claims or any other portion of the originally filed specification. *See In re Koller*, 613 F.2d 819, 204 USPQ 702 (CCPA 1980) (original claims constitute their own description); *accord In re Gardner*, 475 F.2d 1389, 177 USPQ 396 (CCPA 1973); *accord In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). Written description for each element of claim 136 is found, for example, in original claim 135, at page 15, lines 21-25 and page 30 lines 18-29 continuing to page 31 lines 1-18 of the application. Additional exemplary support in the application for pending claims 136 and 140-189 is given in the Table at pages 11-12 of the

Preliminary Amendment filed on July 8, 2004. In addition, exemplary support in the application for claims 190-193 is given in the following table.

Claim(s)	Exemplary Support in the Application
190	Page 24, line 3.
191	Page 24, lines 5-8.
192	Page 24, lines 9-30 continuing through page 29, lines 1-2.
193	Page 28, lines 25-28.

Accordingly, Applicants have satisfied their burden under 35 U.S.C. § 112, first paragraph, and withdrawal of this ground for rejection is respectfully requested.

V. Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date April 12, 2007

By _____ 35,087 for

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A. Disclosed Fenofibrate Formulations that Meet the Limitations of Applicants' Claims				
Example	**Quantity of Fenofibtrate**	**Identity and Quantity of Surface Stabilizer(s)**	**Particle Size**	**Redispersion Testing**
1	Formulation 1 comprised 5% (w/w) fenofibrate	1% (w/w) hypromellose, and 0.05% (w/w) dioctyl sodium sulfosuccinate (DOSS)	Mean: 139 nm 90% < 266 nm	In three different simulated biological fluids, (electrolyte test media #1, #2, #3), two showed no agglomeration and 1 showed slight particle agglomeration. After 2 weeks storage in water at 2-8°C, the composition had a mean particle size of 295 nm, and a D90 of < 386 nm, demonstrating a stable composition.
2	Formulation 4 comprised 5% (w/w) fenofibrate	1% (w/w) hypromellose, and 0.01% (w/w) DOSS	Mean: 412 nm 90% < 502 nm	In three different electrolyte test media, all 3 showed no agglomeration
3	Fenofibrate:sucrose = 1:0.6	Hypromellose:DOSS = 1:0.2		Redispersibility was tested in water and two different electrolyte solutions. In water, the redispersed mean particle size was 390 nm, with a D90 of 374 nm, and 99.7% of the particles < 1 micron. In Electrolyte media #2 and #3, the mean size of the redispersed fenofibrate particles was 258 and 287 nm, the D90 was 374 and 430 nm, and 99.7 and 99.6% of the fenofibrate particles were < 1 micron, respectively.
3	Fenofibrate:sucrose = 1:1	Hypromellose:DOSS +SLS = 1:0.3		Redispersibility was tested in water and two different electrolyte solutions. In water, the redispersed mean particle size was 182 nm, with a D90 of 260 nm, and 100% of the particles < 1 micron. In Electrolyte media #2 and #3, the mean size of the redispersed fenofibrate particles was 193 and 225 nm, the D90 was 276 and 315 nm, respectfully, and 100% of the fenofibrate particles of both compositions were < 1 micron.

A. Disclosed Fenofibrate Formulations that Meet the Limitations of Applicants' Claims				
Example	**Quantity of Fenofibtrate**	**Identity and Quantity of Surface Stabilizer(s)**	**Particle Size**	**Redispersion Testing**
4	Fenofibrate:sucrose = 1:1	Hypromellose:SLS + DOSS = 1:0.45		Redispersibility was tested in water and two different electrolyte solutions. In water, the redispersed mean particle size was 196 nm, with a D90 of 280 nm, and 100% of the particles < 1 micron. In Electrolyte media #2 and #3, the mean size of the redispersed fenofibrate particles was 222, the D90 was 306, and 100% of the fenofibrate particles were < 1 micron.
5 and 6	160 mg fenofibrate	Hypromellose, DOSS, and SLS	Mean = 169 nm	In vivo human testing showing no fed/fasted variability
5, 7 & 8	145 mg fenofibrate (222.54 g/Kg fenofibrate)	Hypromellose, DOSS, SLS (44.506, 4.4378, and 15.585 g/Kg, respectively)	Mean = 169 nm	Dissolution was compared to TRICOR in media representative of in vivo conditions; i.e, "the dissolution medium is predictive of *in vivo* dissolution of a composition." In 12 test samples, the mean dissolution % at 5, 10, 20 and 30 min. was 41.7, 82.6, 100.5, and 102.0%, respectively. In contrast, the conventional, microcrystalline TRICOR shows a mean dissolution % at 5, 10, 20 and 30 min. of 10, 20, 50, and 75%, respectively.

B. Disclosed Fenofibrate Formulations that Do Not Meet the Limitations of Applicants' Claims				
Example	**Quantity of Fenofibtrate**	**Identity and Quantity of Surface Stabilizer(s)**	**Particle Size**	**Redispersion Testing**
1	Formulation 2 comprised 5% (w/w) fenofibrate,	1% (w/w) Pluronic® S-630 (a random copolymer of vinyl acetate and vinyl pyrrolidone), and 0.05% (w/w) DOSS	Mean: 233 nm 90% < 355 nm	In three different electrolyte test media, heavy agglomeration was found in 1 media, slight agglomeration in another. This formulation was not very stable in water.
2	Formulation 3 comprised 5% (w/w) fenofibrate	1% (w/w) hydroxypropylcellulose SL (HPC-SL), and 0.01% (w/w) DOSS	Mean: 696 nm 90% < 2086 nm	Not tested
2	Formulation 5 comprised 5% (w/w) fenofibrate	1% (w/w) polyvinylpyrrolidone (PVP K29/32), and 0.01% (w/w) DOSS	Mean: 4120 nm 90% < 9162 nm	Not Tested
2	Formulation 6 comprised 5% (w/w) fenofibrate	1% (w/w) Pluronic® S-630, and 0.01% (w/w) DOSS	Mean: 750 nm 90% < 2184 nm	In three different electrolyte test media, 1 showed agglomeration, 1 showed very slight agglomeration, and 1 showed slight agglomeration